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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/EP99/07132 (22) International Filing Date: 27 September 1999 (27.09.99) (30) Priority Data: 9821000.8 28 September 1998 (28.09.98) GB (71) Applicant (for all designated States except US): GLAXO GROUP LIMITED [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): MCDADE, Hugh, Brownlie [GB/GB]; Glaxo Wellcome plc, Greenford Road, Greenford, Middlesex UB6 0NN (GB). SMILEY, Margaret, Lynn [US/US]; Glaxo Wellcome Inc., Five Moore Drive, Research Triangle Park, NC 27709 (US). ST. CLAIR, Martha, Heider [US/US]; Glaxo Wellcome Inc., Five Moore Drive, Research Triangle Park, NC 27709 (US). (74) Agent: QUILLIN, Helen, K.; Glaxo Wellcome plc, Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>Without international search report and to be republished upon receipt of that report.</i>
(54) Title: ANTIVIRAL COMBINATIONS COMPRISING (S)-2- ETHYL-7- FLUORO-3- OXO-3,4- DIHYDRO-2H- QUINOXALINE-1- CARBOXYLIC ACID ISOPROPYL ESTER (57) Abstract The present invention relates to therapeutic combinations comprising (S)-2-ethyl-7- fluoro-3- oxo-3, 4-dihydro- 2H-quinoxaline -1-carboxylic acid isopropyl ester and a second therapeutic agent selected from 3'-azido-3' -deoxythymidine (zidovudine) and (2R,cis)-4-amino-1- (2-hydroxymethyl -1,3-oxathiolan -5-yl)-(1H) -pyrimidin -2-one (lamivudine). The present invention is also concerned with pharmaceutical compositions containing said combinations and their use in the treatment of HIV infections including infections with HIV mutants bearing resistance to nucleoside and/or non-nucleoside inhibitors of the replication of HIV.		

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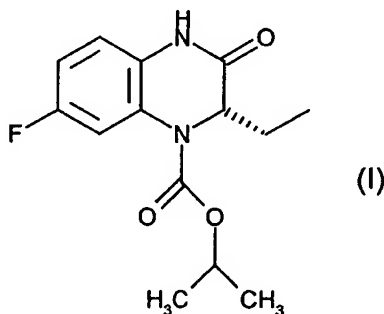
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ANTIVIRAL COMBINATIONS COMPRISING (S)-2-ETHYL-7-FLUORO-3-OXO-3,4-DIHYDRO-2H-QUINOXALINE-1-CARBOXYLIC ACID ISOPROPYL ESTER

The present invention relates to therapeutic combinations comprising (S)-2-ethyl-7-fluoro-3-oxo-3,4-dihydro-2H-quinoxaline-1-carboxylic acid isopropyl ester and a second therapeutic agent selected from 3'-azido-3'-deoxythymidine (zidovudine, AZT™) and (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one (lamivudine, 3TC™). The present invention is also concerned with pharmaceutical compositions containing said combinations and their use in the treatment of HIV infections including infections with HIV mutants bearing resistance to nucleoside and/or non-nucleoside inhibitors of the replication of HIV.

Throughout the specification and the claims which follow, unless the context requires otherwise, the word 'comprise', and variations such as 'comprises' and 'comprising', will be understood to imply the inclusion of a stated integer or step or group of integers but not to the exclusion of any other integer or step or group of integers or steps.

(S)-2-Ethyl-7-fluoro-3-oxo-3,4-dihydro-2H-quinoxaline-1-carboxylic acid isopropyl ester, (I)



which may also be referred to as (S)-1-methylethyl 2-ethyl-7-fluoro-3,4-dihydro-3-oxo-1-(2H)-quinoxalinecarboxylate, (European patent applications nos. 059398 and 078093) is a non-nucleoside reverse transcriptase inhibitor useful in the treatment of HIV.

5 Zidovudine and lamivudine are now well established as important and useful chemotherapeutic agents for the treatment and/or prophylaxis of HIV-infections including related clinical conditions such as AIDS, AIDS-related complex (ARC), AIDS dementia complex (ADC) and also for the treatment of patients who have an asymptomatic HIV infection or who are anti-HIV antibody-positive. Treatment with zidovudine or lamivudine prolongs the disease-free interval in asymptomatic patients infected with HIV and delays death in symptomatic patients.

10 Combinations of, inter alia, zidovudine or lamivudine with quinoxaline non-nucleoside reverse transcriptase inhibitors of a genus including (S)-2-ethyl-7-fluoro-3-oxo-3,4-dihydro-2H-quinoxaline-1-carboxylic acid isopropyl ester are disclosed in European patent application no. 0657166. There is no specific disclosure of combinations comprising (S)-2-ethyl-7-fluoro-3-oxo-3,4-dihydro-2H-quinoxaline-1-carboxylic acid isopropyl ester.

15 It has now been found that by combining (S)-2-ethyl-7-fluoro-3-oxo-3,4-dihydro-2H-quinoxaline-1-carboxylic acid isopropyl ester and lamivudine or zidovudine, a synergistic anti-HIV effect is achieved. It is a feature of this invention that the use of such a drug combination will provide one or more of the following effects :
20 synergistic antiviral effects, more complete viral suppression, viral suppression over a longer period, limit the emergence of drug resistant HIV mutants, and/or allow better management of drug-related toxicities.

25 According to one aspect of the invention there is provided a combination comprising (S)-2-ethyl-7-fluoro-3-oxo-3,4-dihydro-2H-quinoxaline-1-carboxylic acid isopropyl ester, or a physiologically functional derivative thereof, and a reverse transcriptase inhibitor selected from lamivudine and its physiologically functional derivatives and zidovudine and its physiologically functional derivatives.

30 A further feature of the present invention is a triple combination comprising (S)-2-ethyl-7-fluoro-3-oxo-3,4-dihydro-2H-quinoxaline-1-carboxylic acid isopropyl ester, or a physiologically functional derivative thereof, lamivudine or a physiologically functional derivative thereof and zidovudine or a physiologically functional derivative thereof. The ratios of the components of such
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combinations will conveniently be the same as the ratios of the relevant compounds in the double combinations of the invention.

5 As used herein, the term "physiologically functional derivative" includes any physiologically acceptable solvate, salt, ether, ester, salt of such ester, or solvates of any such salt, ether or ester, of (S)-2-ethyl-7-fluoro-3-oxo-3,4-dihydro-2H-quinoxaline-1-carboxylic acid isopropyl ester, or lamivudine or zidovudine; or any other compound which upon administration to the recipient, is capable of providing (directly or indirectly) such a compound or an antivirally
10 active metabolite or residue thereof.

Preferred esters in accordance with the invention are independently selected from the following group: (1) carboxylic acid esters in which the non-carbonyl moiety of the carboxylic acid portion of the ester grouping is selected from
15 straight or branched chain alkyl (for example, methyl, n-propyl, t-butyl, or n-butyl), cycloalkyl, alkoxyalkyl (for example, methoxymethyl), aralkyl (for example, benzyl), aryloxyalkyl (for example, phenoxymethyl), aryl (for example, phenyl optionally substituted by, for example, halogen, C₁₋₄ alkyl, or C₁₋₄ alkoxy), or amino; (2) sulphonate esters, such as alkyl- or aralkylsulphonyl (for example, methanesulphonyl); (3) amino acid esters (for example, L-valyl or L-isoleucyl);
20 and (4) phosphonate esters. In such esters, unless otherwise specified, any alkyl moiety present advantageously contains from 1 to 18 carbon atoms, particularly from 1 to 6 carbon atoms, more particularly from 1 to 4 carbon atoms. Any cycloalkyl moiety present in such esters advantageously contains
25 from 3 to 6 carbon atoms. Any aryl moiety present in such esters advantageously comprises a phenyl group. Any reference to any of the above compounds also includes a reference to a physiologically acceptable salt thereof.

30 Examples of physiologically acceptable salts include salts derived from an appropriate base, such as an alkali metal (for example, sodium), an alkaline earth (for example, magnesium), ammonium and NX_4^+ (wherein X is C₁₋₄ alkyl). Salts of acids or bases which are not physiologically acceptable may also find use, for example, in the preparation or purification of a physiologically

acceptable compound. All salts, whether or not derived from a physiologically acceptable acid or base, are within the scope of the present invention.

5 Combinations of (S)-2-ethyl-7-fluoro-3-oxo-3,4-dihydro-2H-quinoxaline-1-carboxylic acid isopropyl ester, or a physiologically functional derivative thereof, and lamivudine and/or zidovudine, or physiologically functional derivatives thereof, may hereinafter be referred to as combinations according to the invention.

10 The present invention further provides combinations according to the invention for use in the treatment of an HIV infection including infections with HIV mutants bearing resistance to nucleoside inhibitors, particularly zidovudine, lamivudine, abacavir, ddl, ddC, DOTC or d4T or combinations thereof and HIV protease inhibitors.

15 According to another aspect, the present invention provides a method for the treatment of an HIV infection in an infected animal, for example, a mammal including a human, which comprises treating said animal with a therapeutically effective amount of a combination of (S)-2-ethyl-7-fluoro-3-oxo-3,4-dihydro-2H-quinoxaline-1-carboxylic acid isopropyl ester, or a physiologically functional derivative thereof, and at least one of lamivudine or a physiologically functional derivative thereof and zidovudine or a physiologically functional derivative thereof.

20 Reference herein to treatment extends to prophylaxis as well as the treatment of established infections or symptoms.

25 It will be appreciated that the compounds of the combination may be administered simultaneously, either in the same or different pharmaceutical formulations or sequentially. If there is sequential administration, the delay in administering the second and any subsequent active ingredient should not be such as to lose the benefit of a synergistic therapeutic effect of the combination of the active ingredients. It will also be understood that the compounds of the combination or the physiologically functional derivatives of any thereof, whether

presented simultaneously or sequentially, may be administered individually or in multiples or in any combination thereof.

5 Lamivudine and zidovudine are available commercially in a unitary dosage form under the trade mark COMBIVIR™. Administration to a patient of COMBIVIR™ and a pharmaceutical formulation comprising (S)-2-ethyl-7-fluoro-3-oxo-3,4-dihydro-2H-quinoxaline-1-carboxylic acid isopropyl ester represents a convenient embodiment of the present invention. Suitably, for combination with COMBIVIR™, (S)-2-ethyl-7-fluoro-3-oxo-3,4-dihydro-2H-quinoxaline-1-carboxylic acid isopropyl ester will be presented as a formulation suitable for oral administration, preferably a tablet comprising, for example, 10 – 1200mg of (S)-2-ethyl-7-fluoro-3-oxo-3,4-dihydro-2H-quinoxaline-1-carboxylic acid isopropyl ester, such as about 20mg of (S)-2-ethyl-7-fluoro-3-oxo-3,4-dihydro-2H-quinoxaline-1-carboxylic acid isopropyl ester.

15 The present invention also provides the use of (S)-2-ethyl-7-fluoro-3-oxo-3,4-dihydro-2H-quinoxaline-1-carboxylic acid isopropyl ester in the manufacture of a medicament for administration simultaneously or sequentially with at least one of lamivudine and zidovudine for the treatment and/or prophylaxis of HIV infections and associated clinical conditions hereinbefore described.

25 The synergistic effects of the combination of (S)-2-ethyl-7-fluoro-3-oxo-3,4-dihydro-2H-quinoxaline-1-carboxylic acid isopropyl ester and lamivudine or zidovudine may be seen over a ratio, for example, of 1: 200 to 200: 1, such as 1:20 to 20:1 to 20 (by weight), preferably 1:10 to 10:1 (by weight).

Conveniently each compound may be employed in the combination in an amount at which it exhibits antiviral activity when used alone.

30 The amount of a combination of (S)-2-ethyl-7-fluoro-3-oxo-3,4-dihydro-2H-quinoxaline-1-carboxylic acid isopropyl ester and lamivudine and/or zidovudine required to be effective as an anti-HIV agent may, of course, vary and is ultimately at the discretion of the medical practitioner. The factors to be considered include the route of administration and nature of the formulation, the

animal's body weight, age and general condition and the nature and severity of the disease to be treated.

5 In general a suitable dose of (S)-2-ethyl-7-fluoro-3-oxo-3,4-dihydro-2H-quinoxaline-1-carboxylic acid isopropyl ester for administration to a human for treatment of an HIV infection may be in the range of 0.1 to 20 mg per kilogram body weight of the recipient per day, preferably in the range of 0.2 to 5 mg per kilogram body weight per day and most preferably in the range 0.2 to 3.5 mg per kilogram body weight per day.

10

In general a suitable dose of zidovudine will be in the range of 2 to 100 mg per kilogram body weight of the recipient per day, preferably in the range of 3 to 50 mg per kilogram body weight per day and most preferably in the range 4 to 12 mg per kilogram body weight per day.

15

For lamivudine a suitable daily dose will be in the range of from about 1 to about 100 mg per kilogram body weight of the recipient per day, preferably in the range of 2 to 40 mg per kilogram body weight per day, most preferably in the range of 3 to 10 mg per kilogram body weight per day.

20

Unless otherwise indicated all weights of active ingredients are calculated in terms of the drug per se. The desired dose may preferably be presented as one, two, three, four, five, six or more sub-doses administered at appropriate intervals throughout the day. These sub-doses may be administered in unit dosage forms, for example, containing from 1 to 1200 mg, preferably from 5 to 1000 mg, most preferably from 10 to 700 mg of active ingredient per unit dosage form. Alternatively, if the condition of the recipient so requires, the dose may be administered as a continuous infusion.

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30 The components of the combination which may be referred to as active ingredients may be administered for therapy to an animal e.g. a mammal including a human in a conventional manner.

35 While it possible for the active ingredients of the combination to be administered as the raw chemical it is preferable to present them as a pharmaceutical

formulation. Pharmaceutical formulations according to the present invention comprise a combination according to the invention together with one or more pharmaceutically acceptable carriers or excipients and optionally other therapeutic agents. The carrier(s) must be acceptable in the sense of being compatible with the other ingredients of the formula and not deleterious to the recipient thereof. When the individual components of the combination are administered separately they are generally each presented as a pharmaceutical formulation. The references hereinafter to formulations refer unless otherwise stated to formulations containing either the combination or a component thereof.

A combination of (S)-2-ethyl-7-fluoro-3-oxo-3,4-dihydro-2H-quinoxaline-1-carboxylic acid isopropyl ester and lamivudine and/or zidovudine or a physiologically functional derivative of any thereof may conveniently be presented as a pharmaceutical formulation in a unitary dosage form. A convenient unitary dosage formulation contains (S)-2-ethyl-7-fluoro-3-oxo-3,4-dihydro-2H-quinoxaline-1-carboxylic acid isopropyl ester in an amount of from 10mg to 1200mg, for example 20mg to 200mg, and lamivudine and/or zidovudine in amounts of from 50mg to 2g each, for example, 100 mg to 600mg. A particularly convenient unitary dosage formulation may contain (S)-2-ethyl-7-fluoro-3-oxo-3,4-dihydro-2H-quinoxaline-1-carboxylic acid isopropyl ester in an amount of from 10-100mg, such as 20-50mg, lamivudine in an amount of 100-200mg, such as 150mg, and zidovudine in an amount of 100-500mg, such as 300mg.

Pharmaceutical formulations are often prescribed to the patient in "patient packs" containing the whole course of treatment in a single package, usually a blister pack. Patient packs have an advantage over traditional prescriptions, where a pharmacist divides a patient's supply of a pharmaceutical from a bulk supply, in that the patient always has access to the package insert contained in the patient pack, normally missing in traditional prescriptions. The inclusion of a package insert has been shown to improve patient compliance with the physician's instructions and, therefore, lead generally to more successful treatment.

It will be understood that the administration of the combination of the invention by means of a single patient pack, or patient packs of each formulation, containing within a package insert instructing the patient to the correct use of the invention is a desirable additional feature of this invention.

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According to a further aspect of the invention provided is a multiple, for example, double or triple, pack comprising at least (S)-2-ethyl-7-fluoro-3-oxo-3,4-dihydro-2H-quinoxaline-1-carboxylic acid isopropyl ester and lamivudine or zidovudine and an information insert containing directions on the use of the combination of the invention.

10

A particularly convenient patient pack for use in accordance with the present invention comprises (S)-2-ethyl-7-fluoro-3-oxo-3,4-dihydro-2H-quinoxaline-1-carboxylic acid isopropyl ester in a formulation suitable for oral administration, for example a tablet, and COMBIVIR™.

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Formulations include those suitable for oral, rectal, nasal, topical (including transdermal, buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous and intradermal) administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. Such methods represent a further feature of the present invention and include the step of bringing into association the active ingredients with the carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association the active ingredients with liquid carriers or finely divided solid carriers or both, and then if necessary shaping the product.

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Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, caplets, cachets or tablets each containing a predetermined amount of the active ingredients; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

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A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredients in a free-flowing form such as a powder or granules, optionally mixed with a binder (e.g. povidone, gelatin, hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (e.g. sodium starch glycollate, cross-linked povidone, cross-linked sodium carboxymethyl cellulose) surface-active or dispersing agent. Moulded tablets may be made by moulding a mixture of the powdered compound moistened with an inert liquid diluent in a suitable machine. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredients therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile. Tablets may optionally be provided with an enteric coating, to provide release in parts of the gut other than the stomach.

Formulations suitable for topical administration in the mouth include lozenges comprising the active ingredients in a flavored base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier. Formulations for rectal administration may be presented as a suppository with a suitable base comprising, for example, cocoa butter or a salicylate.

Topical administration may also be by means of a transdermal iontophoretic device.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Pharmaceutical formulations suitable for rectal administration wherein the carrier is a solid are most preferably presented as unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art. The suppositories may be conveniently formed by admixture of the active

combination with the softened or melted carrier(s) followed by chilling and shaping in moulds.

5 Formulations suitable for parenteral administration include aqueous and nonaqueous isotonic sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents; and liposomes or other microparticulate systems which are designed to target the
10 compound to blood components or one or more organs. The formulations may be presented in unit-dose or multi-dose sealed containers, for example, ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injection, immediately prior to use. Extemporaneous injection solutions and
15 suspensions may be prepared from sterile powders, granules and tablets of the kind previously described. Formulations may be prepared suitable for continuous infusion by methods known in the art.

20 Preferred unit dosage formulations are those containing a daily dose or daily subdose of the active ingredients, as hereinbefore recited, or an appropriate fraction thereof.

Pharmaceutical formulations suitable for oral administration are preferred. Particularly preferred are tablets for oral administration.

25 It should be understood that in addition to the ingredients particularly mentioned above the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example, those suitable for oral administration may include such further agents as sweeteners, thickeners and flavoring agents.
30

It will be further understood that the combinations of the invention may be combined with one or more other HIV anti-viral agents, for example other Reverse Transcriptase Inhibitors (RTIs), other Non Nucleoside Reverse
35 Transcriptase Inhibitor (NNRTIs), HIV protease inhibitors and fusion inhibitors.

The compounds of the combination of the present invention may be obtained in a conventional manner.

- 5 (S)-2-ethyl-7-fluoro-3-oxo-3,4-dihydro-2H-quinoxaline-1-carboxylic acid isopropyl ester may be prepared by the method described in European Specification EP0509398 and EP078093 which are incorporated herein by reference.

- 10 Zidovudine can be prepared, for example, as described in U.S. Patent 4724232, incorporated herein by reference. Zidovudine can also be obtained from Aldrich Chemical Co., Milwaukee, WI 53233, USA.

Methods for the preparation of lamivudine are described in International Patent Applications Numbers. WO91/17159, WO92/20669 and WO 95/29174, incorporated herein by reference.

- 15 The following examples are intended for illustration only and are not intended to limit the scope of the invention in any way. "Active ingredient" denotes (S)-2-ethyl-7-fluoro-3-oxo-3,4-dihydro-2H-quinoxaline-1-carboxylic acid isopropyl ester, lamivudine, zidovudine or multiples thereof or a physiologically functional
20 derivative of any of the aforementioned compounds.

Example 1: Tablet Formulation

- 25 The following formulations are prepared by wet granulation of the ingredients with a solution of povidone, followed by addition of magnesium stearate and compression.

	<u>mg/tablet</u>
Active Ingredient	250
Lactose B.P.	210
30 Povidone B.P.	15
Sodium Starch Glycollate	20
Magnesium Stearate	5
	<hr/>
	500

12

The following formulations are prepared by direct compression of the admixed ingredients.

	<u>mg/tablet</u>
5	
Active Ingredient	250
Pregelatinized Starch NF15	150
	<hr/>
	400

10

Controlled Release Formulation

The formulation is prepared by wet granulation of the ingredients with a solution of povidone followed by the addition of magnesium stearate and compression.

15

	<u>mg/tablet</u>
Active Ingredient	500
Hydroxypropylmethylcellulose	112
20 (Methocel K4M Premium)	
Lactose B.P.	53
Povidone B.P.	28
Magnesium Stearate	7
	<hr/>
25	700

Drug release takes place over a period of about 6-8 hours and is complete after 12 hours.

30

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Example 2: Capsule Formulations

	<u>mg/capsule</u>
5 Active Ingredient	250
Macrogl 4000 B.P.	350
	<hr/>
	600

- 10 Capsules are prepared by melting the Macrogl 4000 B.P., dispersing the active ingredient in the melt and filling the melt into a two-part hard gelatin capsule.

Controlled Release Capsule

- 15 The following controlled release capsule formulation is prepared by extruding ingredients a, b, and c using an extruder, followed by spheronization of the extrudate and drying. The dried pellets are then coated with release-controlling membrane (d) and filled into a two-piece, hard gelatin capsule.

20

	<u>mg/capsule</u>
(a) Active Ingredient	250
(b) Microcrystalline Cellulose	125
25 (c) Lactose B.P.	125
(d) Ethyl Cellulose	13
	<hr/>
	513

30

35

Example 3: Injectable Formulation

		<u>mg</u>
	Active Ingredient	200
5	Hydro chloric Acid Solution 0.1M or	
	Sodium Hydroxide Solution 0.1M q.s. to pH	4.0 to 7.0
	Sterile water q.s. to	10 ml

10 The active ingredient is dissolved in most of the water (35° - 40° C) and the pH adjusted to between 4.0 and 7.0 with the hydrochloric acid or the sodium hydroxide as appropriate. The batch is then made up to volume with water and filtered through a sterile micropore filter into a sterile 10 ml amber glass vial (type 1) and sealed with sterile closures and overseals.

15 Example 4: Intramuscular Injection

	Active Ingredient	200 mg
	Benzyl Alcohol	0.10 g
	Glycofurol 75	1.45 g
20	Water for injection q.s. to	3.00 ml

25 The active ingredient is dissolved in the glycofurol. The benzyl alcohol is then added and dissolved, and water added to 3 ml. The mixture is then filtered through a sterile micropore filter and sealed in sterile 3 ml amber glass vials (type 1).

Example 5: Syrup

	Active Ingredient	250 mg
30	Sorbitol Solution	1.50 g
	Glycerol	2.00 g
	Sodium Benzoate	0.005 g
	Flavor, Peach 17.42.3169	0.0125 ml
	Purified Water q.s. to	5.00 ml

35

The active ingredient is dissolved in a mixture of the glycerol and most of the purified water. An aqueous solution of the sodium benzoate is then added to the solution, followed by addition of the sorbitol solution and finally the flavor. The volume is made up with purified water and mixed well.

5

Example 6: Suppository

	<u>mg/capsule suppository</u>
Active Ingredient	250
10 Hard Fat, B.P. (Witepsol H15-Dynamit Nobel)	1770
	<hr/>
	2020

One-fifth of the Witepsol H15 is melted in a steam-jacketed pan at 45°C maximum. The active ingredient is sifted through a 200µm sieve and added to the molten base with mixing, using a Silverson fitted with a cutting head, until a smooth dispersion is achieved. Maintaining the mixture at 45° C, the remaining Witepsol H15 is added to the suspension and stirred to ensure a homogenous mix. The entire suspension is passed through a 250µm stainless steel screen and, with continuous stirring, is allowed to cool to 45° C. At a temperature of 38° C to 40° C, 2.02 g of the mixture is filled into suitable, 2 ml plastic moulds. The suppositories are allowed to cool to room temperature.

Example 7: Pessaries

25

	<u>mg/pessary</u>
Active Ingredient	250
Anhydrate Dextrose	380
30 Potato Starch	363
Magnesium Stearate	7
	<hr/>
	1000

The above ingredients are mixed directly and pessaries prepared by direct compression of the resulting mixture.

5

Biological Data

Example 8

10 MT4 cells were infected with HIV-1 3B and, after a 1 hour incubation, were exposed to combinations of (S)-2-ethyl-7-fluoro-3-oxo-3,4-dihydro-2H-quinoxaline-1-carboxylic acid isopropyl ester (COMPOUND A) and lamivudine (3TC) or zidovudine (AZT). Five days later, the cytopathic effect was quantitated using a standard propidium iodide assay. Based on the calculated fractional
15 inhibitory concentrations (Figure 1), (S)-2-ethyl-7-fluoro-3-oxo-3,4-dihydro-2H-quinoxaline-1-carboxylic acid isopropyl ester is seen to be synergistic with each of lamivudine and zidovudine.

Example 9

20

Cell cultures were performed in 25cm² cell culture bottles containing 5 ml of HIV-1 (IIIB)-infected CEM cells (at 250,000 cells/ml). The drug concentrations were not increased during 12 subsequent subcultivations. Cell cultures that did not show giant cell formation after 12 subcultivations were further passaged for at
25 least an additional 3 subcultivations in the absence of test compounds and p24 antigen assays were performed on the supernatants of these cultures to confirm the lack of virus production.

30 Mutant HIV-1 strains emerging from the combination experiments were tested for their sensitivities against test compounds and analysed for the presence of resistance-conferring mutations in their pol genes.

When compared to the single drug controls, the paired combinations of GW420867X with 3TC resulted in a pronounced (synergistic) retardation of virus
35 breakthrough (Table 1)

Table 1

5

		GW420867X (µg/ml)				
		0.01	0.005	0.0025	0.001	0
3TC (µg/ml)		Time to virus breakthrough [days]				
0.1		>42	>42	>42	17	6
0.04		>42	37	7	6	5
0.02		28	20	6	4	3
Control-1 (None)	0	12	11	6	5	2
Control-2 (None)	0	16	9	6	4	2

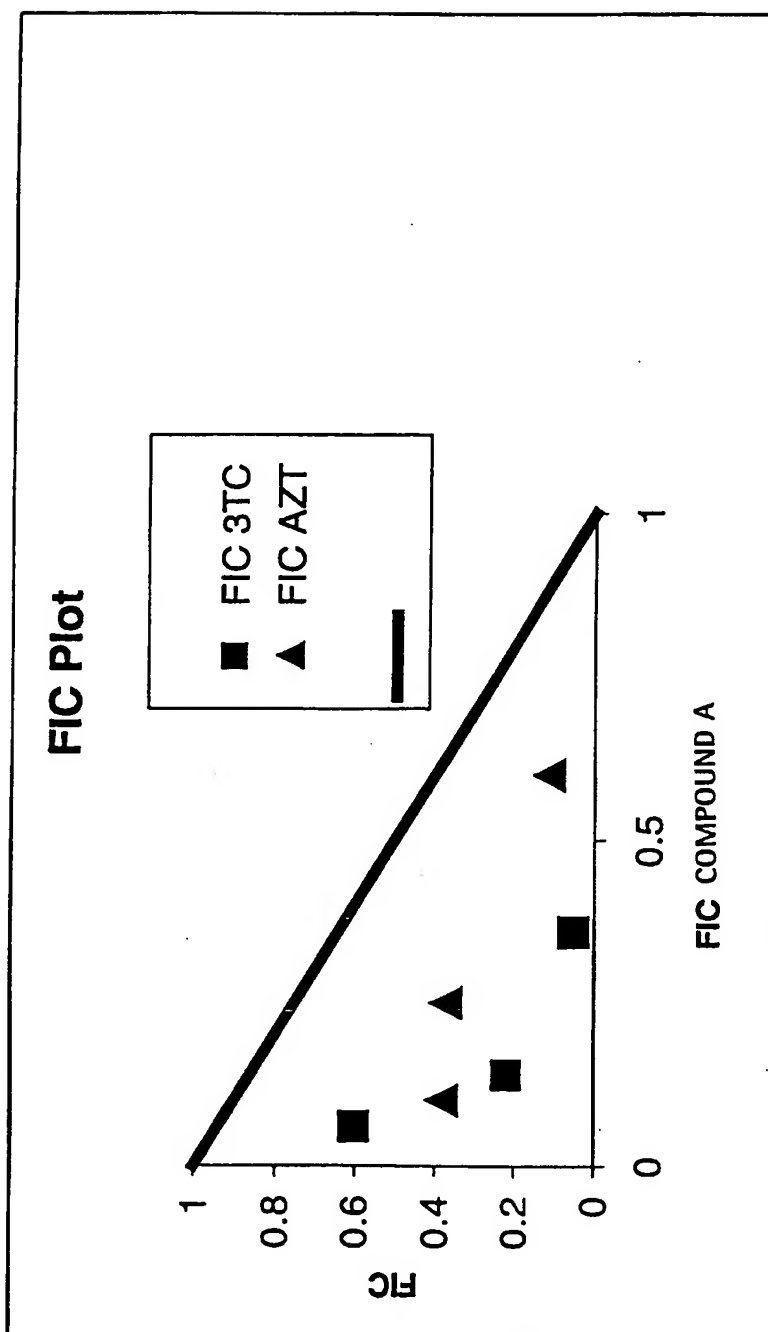
CLAIMS

1. A combination comprising (S)-2-ethyl-7-fluoro-3-oxo-3,4-dihydro-2H-
5 quinoxaline-1-carboxylic acid isopropyl ester or a physiologically functional
derivative thereof and a second therapeutic agent selected from 3'-azido-3'-
deoxythymidine (zidovudine) or a physiologically functional derivative thereof
and (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-
one (lamivudine) or a physiologically functional derivative thereof.
10
2. A combination comprising (S)-2-ethyl-7-fluoro-3-oxo-3,4-dihydro-2H-
quinoxaline-1-carboxylic acid isopropyl ester and lamivudine.
3. A combination comprising (S)-2-ethyl-7-fluoro-3-oxo-3,4-dihydro-2H-
15 quinoxaline-1-carboxylic acid isopropyl ester and zidovudine.
4. A combination comprising (S)-2-ethyl-7-fluoro-3-oxo-3,4-dihydro-2H-
quinoxaline-1-carboxylic acid isopropyl ester, or a physiologically functional
derivative thereof, zidovudine or a physiologically functional derivative thereof
20 and lamivudine or a physiologically functional derivative thereof.
5. A combination according to any of claims 1 to 4 for use in medical
therapy.
- 25 6. A pharmaceutical formulation comprising a combination according to any
of claims 1 to 4 together with one or more pharmaceutically acceptable carriers
therefor.
7. A formulation according to claim 6 in unit dosage form.
30
8. A method for the treatment of an HIV infection in an animal subject which
comprises treating said animal subject with a therapeutically effective amount of
a combination as defined in any claim from 1 to 4.

9. A method according to claim 8 wherein the combination is administered as a single combined formulation.
- 5 10. A method according to claim 8 wherein (S)-2-ethyl-7-fluoro-3-oxo-3,4-dihydro-2H-quinoxaline-1-carboxylic acid isopropyl ester or a physiologically functional derivative thereof is administered in combination with COMBIVIR™.
- 10 11. Use of (S)-2-ethyl-7-fluoro-3-oxo-3,4-dihydro-2H-quinoxaline-1-carboxylic acid isopropyl ester or a physiologically functional derivative thereof for the manufacture of a medicament for administration either simultaneously or sequentially with lamivudine or a physiologically functional derivative thereof and/or zidovudine or a physiologically functional derivative thereof for the treatment of an HIV infection.
- 15 12. A patient pack comprising (S)-2-ethyl-7-fluoro-3-oxo-3,4-dihydro-2H-quinoxaline-1-carboxylic acid isopropyl ester or a physiologically functional derivative thereof and zidovudine or a physiologically functional derivative thereof or lamivudine or a physiologically functional derivative thereof.

1 / 1

FIG. 1



INTERNATIONAL SEARCH REPORT

Int. l. Application No

PCT/EP 99/07132

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 A61K31/70 A61K31/495 //(A61K31/70,31:495)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 197 03 131 A (BAYER AG) 30 July 1998 (1998-07-30) page 11, line 60 -page 12, line 10 page 12, line 77 -page 13, line 5 page 13, line 47-58 claims 1,5,6	1-6,8,9
Y	---	7,10-12
Y	EP 0 657 166 A (HOECHST AG) 14 June 1995 (1995-06-14) cited in the application page 67 -page 68 claims 1,2,4-7 ---	7,10-12
	-/--	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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"&" document member of the same patent family

Date of the actual completion of the international search

18 April 2000

Date of mailing of the international search report

28/04/2000

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 99/07132

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>BALZARINI ET AL.: "Retention of marked sensitivity to HBY 097 by an AZT-resistant human immunodeficiency virus type 1 strain subcultured in the combined presence of quinoxaline HBY 097 and lamivudine." BIOCHEMICAL PHARMACOLOGY, vol. 55, 1 March 1998 (1998-03-01), pages 617-625, XP000885674 Belgium abstract page 618; figure 1 page 620 page 624</p>	1-12
A	<p>--- BALZARINI ET AL.: "Zidovudine resistant HIV-1 strains subcultured in the presence of both lamivudine and quinoxaline HBY 097 retain marked sensitivity to HBY 097 but not to lamivudine." JOURNAL OF INFECTIOUS DISEASES, vol. 176, 1997, pages 1392-1397, XP000885682 abstract page 1393 page 1394, left-hand column page 1396, right-hand column</p>	1-12
A	<p>--- BALZARINI ET AL.: "The thiocarboxanilides UC-10 and UC-781 have an additive inhibitory effect against human immunodeficiency virus type 1 reverse transcriptase and replication in cell culture when combined with other antiretroviral drugs." ANTIVIRAL CHEMISTRY AND CHEMOTHERAPY, vol. 8, 1997, pages 197-204, XP000885652 abstract page 203</p> <p>-----</p>	1-12

INTERNATIONAL SEARCH REPORT

Information on patent family members

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